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Original article

Aspirin possibly reduces cerebrovascular events in type 2 diabetic patients with higher C-reactive protein level: Subanalysis from the JPAD Trial

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A B S T R A C T

Background and purpose: There are few data that demonstrate a significant effect of aspirin therapy for diabetic patients as primary prevention for cardiovascular events. A guideline recommends the use of aspirin as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk including those who have additional risk factors. To clarify the effect of primary prevention with aspirin therapy on diabetic patients, the relationship between C-reactive protein (CRP) and the incidence of atherosclerotic events was investigated in participants in the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial.
Methods and subjects: We divided the JPAD participants according to the CRP level at enrollment; CRP ≥ 0.1 mg/dl: high CRP group, CRP < 0.1 mg/dl: low CRP group. The high CRP group consisted of 1131 patients and the low CRP group consisted of 398 patients.
Essential results: There was no significant difference in the incidence of primary atherosclerotic events between the high CRP group and the low CRP group. Of the atherosclerotic events, the incidence of cerebrovascular events, however, was significantly higher in the high CRP group than in the low CRP group. The incidence of cerebrovascular events was higher in the high CRP group than in the low CRP group in patients without aspirin therapy, although there was no significant difference in the incidence of the cerebrovascular events between the high CRP group and the low CRP group in patients undergoing aspirin therapy.
Principal conclusions: Aspirin therapy may reduce cerebrovascular events in diabetic patients with higher CRP. Aspirin therapy could be an additional strategy as primary prevention for diabetic patients with higher CRP.

Introduction

It has been reported that atherosclerosis is the results of several pathogenic factors including inflammatory changes [1] and increased levels of inflammatory markers such as C-reactive protein (CRP) may reflect vascular complications and predict future

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events [2–6]. Diabetes mellitus is also a powerful risk factor for cardiovascular events [7–13]. The American Diabetes Association recommends the use of aspirin as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk, including those who are older than 50 years or who have additional risk factors [14]. However, there are few reports that demonstrate a significant effect of aspirin therapy for diabetic patients as a primary prevention for cardiovascular events. A previous meta-analysis (287 trials, 135,000 participants) on the efficacy of antiplatelet therapy in the prevention of major cardiovascular events found a clear benefit for aspirin, but no statistically significant benefit in the subgroup of only people with diabetes (9 trials, 5126 participants) [15]. No significant reduction in the risk of major cardiovascular events with low-dose aspirin compared with placebo was found in two trials published after the above-mentioned meta-analysis [16,17]. We undertook the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in type 2 diabetic patients [18]. A clear benefit for aspirin in the primary prevention of major cardiovascular events in patients with diabetes remains to be elucidated [18,19]. Therefore, we sought to investigate whether aspirin therapy was effective for diabetic patients with higher CRP levels.

Materials and methods

The JPAD trial design and overall findings have been reported previously [18]. The study protocol is in agreement with the guidelines of the ethics committees at our institutions and the study complies with the 1975 Declaration of Helsinki. Briefly, this multicenter, prospective, randomized, open, blinded end-point study was conducted at 163 institutions throughout Japan, which enrolled 2539 patients with type 2 diabetes, without a history of atherosclerotic disease. The institutional review board at each participating hospital approved this trial, and written informed consent was obtained from each patient. In the JPAD trial, the inclusion criteria were diagnosis of type 2 diabetes mellitus, age between 30 and 85 years, and ability to provide informed consent. The exclusion criteria were electrocardiographic ischemic changes, a history of coronary heart disease, cerebrovascular disease, arteriosclerotic disease, atrial fibrillation, use of antiplatelet or antithrombotic therapy, a history of severe gastric or duodenal ulcer, severe liver dysfunction, severe renal dysfunction, and allergy to aspirin [18]. A total of 2539 patients were randomly assigned as follows: 1262 patients in the aspirin group; and 1277 patients in the nonaspirin group. The median follow-up period was 4.37 years.

It was reported in the Women's Health Study that median CRP level in Asians was 0.112 mg/dl and that this value was lower than that in black women, Hispanic women, and white women [20]. A recent Japanese study also used a CRP level of 0.1 mg/dl to stratify the patients [21]. In this subanalysis, therefore, we divided the JPAD participants according to the CRP levels at enrollment (CRP ≥ 0.1 mg/dl, High CRP group; CRP < 0.1 mg/dl, Low CRP group). The high CRP group consisted of 1131 patients and the low CRP group consisted of 398 patients. We conducted atherosclerotic events analyses and subgroup analyses of atherosclerotic events: cerebrovascular events, including stroke and transient ischemic attack; coronary events, including myocardial infarction and angina; and, aortic and peripheral vascular events.

Definition of atherosclerotic event

The primary end point was any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) during the follow-up period. All potential end points were adjudicated by an independent committee on validation of data and events that were unaware of the group assignments.

Presentation of hemoglobin A1c level

Hemoglobin A1c values were converted from the Japanese Diabetes Society (JDS) values used in the main analysis of the JPAD trial into National Glycoprotein Standardization Program (NGSP) equivalent values. NGSP equivalent values were calculated using the following formula: NGSP equivalent value (%) = JDS value (%) + 0.4% [22].

Statistical analyses

Efficacy comparisons were performed on the basis of time to the first event, according to the intention-to-treat principle, including all patients in each group to which they were randomized with patients lost to follow-up cut from the study as of their last hospital visit. Following the descriptive statistics, cumulative incidences of primary end points were estimated utilizing the Kaplan–Meier method and differences between groups were then assessed with the log-rank test. The chi-square test was used to compare the frequency data between the groups. We used the Cox proportional hazards analysis to estimate hazards ratios (HRs) of CRP level (CRP ≥ 0.1 mg/dl), with 95% CI. We included the clinically significant factors such as age [18], aspirin [18], CRP, hypertension [23], 90 ml/min/1.73 m^2 > estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2 [24], and 60 ml/min/1.73 m^2 > eGFR [23]. Patients with missing values for any selected variable were excluded from the analyses that used this variable. All statistical analyses were conducted using SAS software Version 9.1 (SAS Institute Inc, Cary, NC, USA). *p*-Values of less than 0.05 were considered statistically significant.

Results

Baseline clinical characteristics

The baseline clinical patient characteristics are shown in Table 1. There were significant differences in body mass index, the frequency of diabetic neuropathy, and proteinuria between the high CRP group and the low CRP group. The use of calcium channel blockers and β-blockers were significantly higher in the high CRP group than low CRP group. The clinical characteristics, such as age, gender, BP, the frequency of smoking, dyslipidemia, diabetic retinopathy, diabetic nephropathy, duration of diabetes, use of statins, and use of drugs for diabetes except for the usage of biguanides, were all similar between the high CRP group and the low CRP group.

High CRP is not a risk for atherosclerotic events in diabetic patients

There was no significant difference in the incidence of the primary atherosclerotic events between the high CRP group and the low CRP group (HR, 1.31; 95% CI, 0.83–2.15; log-rank test, $p = 0.26$).

Subgroup analyses of cerebrovascular events, coronary events, and aortic and peripheral vascular events

The atherosclerotic events are shown in Table 2. The occurrence and incidence rates of cerebrovascular events was significantly higher in the high CRP group (44 events, 3.9%) than in the low CRP group (7 events, 1.8%) (HR, 2.29; 95% CI, 1.10–5.57; log-rank

Table 1
Baseline characteristics.

Characteristics	High CRP group ($n = 1139$)	Low CRP group ($n = 398$)	p-Value
Age (years)	65 ± 10	64 ± 10	0.1
Male	620 (55)	222 (56)	0.7
Systolic blood pressure (mmHg)	135 ± 15	134 ± 16	0.3
Diastolic blood pressure (mmHg)	77 ± 9	76 ± 9	0.2
Body mass index (kg/m^2)	25 ± 4	24 ± 3	0.0007
Current smoker	253 (22)	88 (22)	0.9
Past smoker	475 (42)	167 (42)	0.98
Dyslipidemia	600 (53)	213 (54)	0.9
Duration of diabetes, median,	2397	2427	0.6
IQR (days)	1017–4539	984–4162	
Diabetic retinopathy	153 (14)	57 (14)	0.7
Diabetic nephropathy	139 (12)	58 (15)	0.2
Proteinuria	219 (20)	59 (15)	0.04
Diabetic neuropathy	112 (10)	62 (16)	0.002
Dermal ulcer	3 (0.3)	4 (1.0)	0.08
Atrial fibrillation	2 (0.2)	1 (0.3)	1
Treatment for hypertension			
Calcium channel blockers	403 (36)	118 (30)	0.03
Angiotensin-II receptor blockers	227 (20)	72 (18)	0.4
Angiotensin-converting enzyme inhibitors	165 (15)	47 (12)	0.2
β-Blockers	97 (9)	18 (5)	0.008
α-Blockers	49 (4)	12 (3)	0.2
Treatment for diabetes and dyslipidemia			
Sulfonylureas	662 (59)	233 (59)	0.5
α-Glucosidase inhibitors	392 (35)	126 (32)	0.3
Biguanides	138 (12)	70 (18)	0.007
Insulin	151 (13)	40 (10)	0.09
Thiazolidines	51 (5)	24 (6)	0.2
Statins	229 (26)	112 (28)	0.5
Family history			
Ischemic heart disease	116 (11)	174 (11)	0.9
Stroke	201 (20)	325 (21)	0.3
Hemoglobin A1c level (%)	7.1 ± 1.4	6.8 ± 1.0	<0.0001
Fasting plasma glucose level (mg/dl)	147 ± 52	140 ± 36	0.003

Data are mean ± SD or n (%). CRP, C-reactive protein; IQR, interquartile range.

test, $p = 0.0361$, Table 2, Fig. 1). Ischemic stroke happened in 29 patients of the high CRP group and in 4 patients of the low group, and hemorrhagic stroke happened in 8 patients of the high CRP group and in 1 patient of the low CRP group. The incidence rate of ischemic stroke events tended to be higher in the high CRP group than in the low CRP group (HR, 2.64; 95% CI, 1.04–8.91; log-rank test, $p = 0.0583$). There were no significant differences, however, in the occurrence rate of coronary events between the high CRP group (2.4%) and the low CRP group (3.5%, Table 2). There was no significant difference in the occurrence rate of aortic and peripheral vascular events between the high CRP group (0.3%) and the low CRP group (0.7%, Table 2). Cox proportional hazards analysis including clinically important factors revealed that age and hypertension were independent predictive factors for cerebrovascular events in type 2 diabetic patients (Table 3). And, CRP was also an important predictive factor for cerebrovascular events in type 2 diabetic patients.

Table 2
Atherosclerotic events.

	High CRP group ($n = 1131$)	Low CRP group ($n = 398$)	p-Value
Coronary events	27 (2.4)	14 (3.5)	0.2
Cerebrovascular events	44 (3.9)	7 (1.8)	0.04
Aortic and peripheral vascular events	8 (0.7)	1 (0.3)	0.5
Death from coronary events	3 (0.3)	0 (0)	0.8
Death from cerebrovascular events	4 (0.3)	1 (0.3)	1
All deaths	28 (2.5)	8 (2.0)	0.6

Data are n (%), CRP, C-reactive protein.

Effect of aspirin therapy on the incidence of cerebrovascular events

We compared the incidence of cerebrovascular events between the patients receiving aspirin therapy and those not receiving aspirin therapy. The incidence of cerebrovascular events was significantly higher in the high CRP group than in the low CRP group (HR, 4.12; 95% CI, 1.22–25.6424; log-rank test, $p = 0.0367$, Fig. 2 Top) in patients not receiving aspirin therapy; there was no significant difference, however, in the incidence rate of cerebrovascular events between the high CRP group and the low CRP group (HR, 1.54; 95% CI, 0.63–4.64; log-rank test, $p = 0.3817$, Fig. 2 Bottom) in patients receiving aspirin therapy.

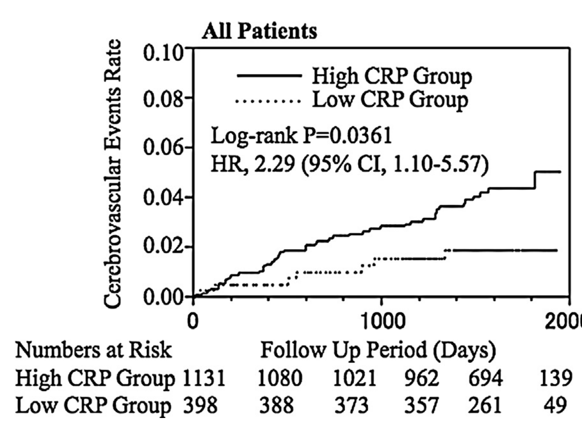

Fig. 1. Comparison of cerebrovascular events between the high C-reactive protein (CRP) group and the low CRP group. The incidence of cerebrovascular events was significantly higher in the high CRP group than in the low CRP group.

Table 3
Multivariate Cox proportional hazards model for cerebrovascular events.

Factor	Hazard ratio	95% CI	*p*-Value
High CRP (CRP ≥ 0.1 mg/dl)	2.21	0.99–4.91	0.052
Use of aspirin	0.92	0.53–1.60	0.789
Age ≥ 65 (years)	2.13	1.14–3.99	0.018
Blood pressure control (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg)	2.24	1.28–3.91	0.005
90 (ml/min/1.73 m^2) > eGFR ≥ 60 (ml/min/1.73 m^2)	2.26	0.87–5.86	0.092
60 (ml/min/1.73 m^2) > eGFR	1.79	0.63–5.07	0.271

CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

Discussion

In the present study, although the incidence of primary atherosclerotic events in type 2 diabetics, consisting of cerebrovascular events, coronary events, and aortic or peripheral vascular events, was not significantly different between the high CRP group and the low CRP group, the incidence of cerebrovascular events was significantly higher in the high CRP group than in the low CRP group. It indicates that CRP may influence the incidence of primary cerebrovascular event in diabetic patients.

Recently, the Antithrombotic Trialists' (ATT) Collaboration undertook a meta-analysis that compared long-term aspirin use versus a non-aspirin control. The meta-analysis result that aspirin therapy yielded a 12% proportional reduction in serious vascular events in the primary prevention trials was reported [25]. However, this study included a small number of diabetic patients. Then, the data do not support the effect of aspirin therapy in the primary prevention of major cardiovascular events in patients with diabetes.

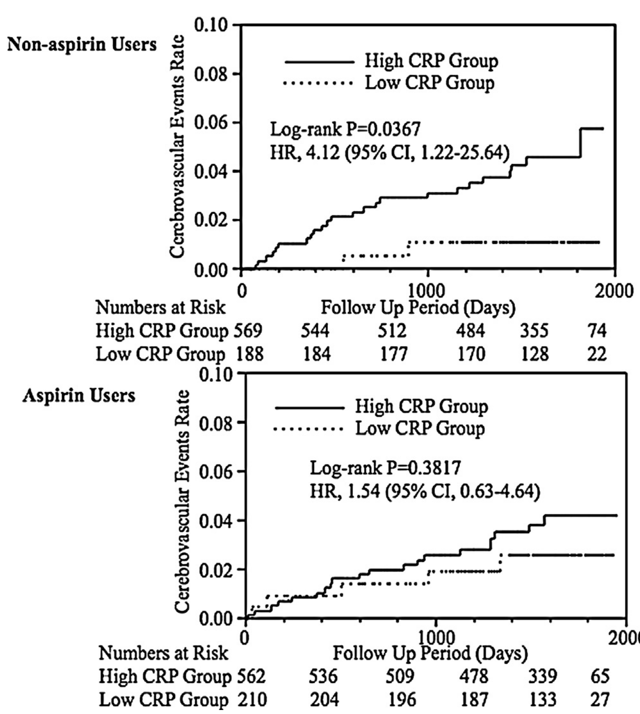

Fig. 2. (Top) Comparison of cerebrovascular events between the high C-reactive protein (CRP) group and the low CRP group without aspirin therapy. The incidence rate of cerebrovascular events was significantly higher in the high CRP group than in the low CRP group in patients not receiving aspirin therapy. (Bottom) Comparison of cerebrovascular events between the high CRP group and the low CRP group with aspirin therapy. The incidence rate of the cerebrovascular events in the high CRP group was as low as the incidence of the low CRP group in patients receiving aspirin therapy.

In the present study, we performed Cox proportional hazards analysis including significant predictive factors because we previously showed significant effect of age, aspirin, hypertension, and eGFR on the incidence of atherosclerotic events in diabetic patients [18,23,24]. The Cox proportional hazards analysis revealed that higher CRP level is not an independent but important predictive factor for cerebrovascular events in type 2 diabetic patients. The incidence of cerebrovascular events was significantly higher in the high CRP group than in the low CRP group in patients without aspirin therapy, although there was no significant difference in the incidence of cerebrovascular events between the high CRP group and the low CRP group in patients with aspirin therapy. It indicates that aspirin therapy may reduce the incidence of cerebrovascular events only in patients with higher CRP level. On the other hand, Cox proportional hazards analysis showed that aspirin is not an independent predictive factor for cerebrovascular events. Therefore, the present study shows the possibility that aspirin reduces cerebrovascular events in diabetic patients with higher CRP levels. To demonstrate the significance of aspirin therapy, we may need a more appropriate control group.

The possible mechanism for the beneficial effect of aspirin therapy on the prevention of cerebrovascular events is inhibition of thrombus formation via blocking thromboxane dependent platelet activation. Elevated CRP levels may reflect the existence of advanced atherosclerosis induced by other cardiovascular risk factors because inflammation is strongly related to atherosclerosis. It is thought that the coexistence of elevated CRP level and other risk factors is a marker of a group at high risk of atherosclerosis, and, thus, the risk of cerebrovascular events is remarkably high in that group. Additionally, recent clinical reviews, as well as experimental and clinical studies, have shown that inflammation is directly associated with the development of atherosclerosis [1] and instability of atheroma [26,27]. It is, therefore, speculated that chronic inflammation directly and extremely enhances the risk of cerebrovascular events by such atherogenic effects of inflammation in people whose arterial walls have already been damaged by other risk factors and aspirin therapy possibly reduces cerebrovascular events.

In the present study, aspirin therapy did not reduce aortic and peripheral vascular events. There are only a few reports that describe the association between aortic and peripheral vascular events and aspirin therapy in diabetic patients. Aspirin therapy did not show any significant preventive effect for cardiovascular events in asymptomatic diabetic patients with lower ankle brachial pressure indexes in the POPADAD Trial [17].

As regards the incidence of coronary events, there were no significant differences between the high CRP group and the low CRP group. This is because the incidence of myocardial infarction was higher in the high CRP group than in the low CRP group, but the incidence of angina was higher in the low CRP group than in the high CRP group. Thus, the influence of higher CRP on the incidence of coronary events appears to be stronger in cases of serious coronary events than in all coronary events. This may be associated with the report that acetylcholine induces coronary spasm and ischemic symptoms were more frequent in aspirin users than in non-users [28].

Study limitations

This subanalysis has a few limitations in addition to those reported in the JPAD Study [18]. The JPAD trial did not achieve the planned statistical power due to the lower incidence of atherosclerotic events than that expected. Because the present study was a subanalysis of the JPAD trial, the number of patients and number of events was lower than the main study. Therefore, the present study is much more underpowered to see the effects of aspirin in the selected subgroups. Thus, a new trial which sets diabetic patients with higher CRP level as the main object is needed.

In conclusion, this study indicates that CRP level influences the incidence of cerebrovascular events in diabetic patients. In the primary prevention of cerebrovascular events, aspirin therapy might have an effect on diabetic patients with higher CRP.

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Appendix A. JPAD Trial Investigators

Hisao Ogawa (principal investigator). *Steering Committee:* Yoshihiko Saito (chair), Masafumi Nakayama, Masao Kanauchi, Shiro Uemura, and Takeshi Morimoto (study statistician). *Committee on Validation of Data and Events:* Izuru Masuda (chair), Dr Nakayama, and Dr Kanauchi. *Safety Monitoring Board:* Hirotsugu Ueshima (chair), Hiroo Imura, and Kazuo Kimura. *Independent Data Management Center:* Makiko Ohtorii and Eri Miyake. *Investigators:* Hideaki Jinnouchi, Yoichi Hanaoka, Masako Waki, Kyousuke Kawamura, Michio Shimabukuro, Kimiaki Nishiura, Takahiro Kawano, Yusuke Kyoda, Jun Hashiguchi, Tadashi Kagoshima, Masakazu Hanatani, Norihiko Matsumura, Naofumi Doi, Kenji Nakai, Yoshiyuki Kobayashi, Megumi Suzuki, Tsuneari Soeda, Yoshinobu Morikawa, Masashi Horimoto, Atsushi Hasegawa, Shigeru Yamano, Syuichi Matsuo, Yasuhiro Sakamoto, Izuru Masuda, Akiko Yasuno, Yuriko Fujinaga, Kazuko Horii, Takeshi Koga, Hiroshi Ogawa, Ken Ozaki, Makoto Ikemura, Motomu Hayashi, Ikuo Yabuta, Kiyotaka Sugihara, Akihiro Yazaki, Joji Masuda, Yoshiharu Nishitani, Masaki Naito, Shigenobu Ote, Kazuhiko Yamada, Chikashi Wakabayashi, Yoshiaki Fukuoka, Keiji Mahara, Hirofumi Kan, Eiji Oshima, Toshio Sutani, Koichi Hoda, Koryo Sawai, Kenichi Yamaga, Tomoki Nakamura, Shinya Okamoto, Hiroaki Horie, Kenichi Ashihara, Hiroshi Miki, Hisaharu Makino, Takafumi Odo, Yoshihisa Iseri (retired in 2007), Hiroyuki Tanaka, Kousuke Marutsuka, Akira Nakatani, Hironori Murakami, Yoshiko Shioya, Yutaka Horio, Tsuneo Ikeda, Kazuo Machii, Masanori Kamura, Keiichiro Ban, Yoshihiro Fujii, Kazuo Nishimoto, Susumu Misugi, Tetsuo Munakata, Katsutoshi Yoshimura, Shigetoshi Minami, Takao Nakashima, Hirofumi Ogata, Atuko Hifumi, Nobuko Sakurai, Ryuichiro Tsurusaki, Yoshito Yamanaka, Hiromitsu Yokota, Seishi Ichihara, Motoki Yoshinari, Yoko Sawada, Eiji Kawashima, Kazuo Goto, Yoshimi Kinoshita, Masao Kikukawa, Hiroharu Yamada, Yuya Tanaka, Mayumi Kiyota, Yoshihiro Kimura, Yasuhiro Morikami, Masahiro Fukuda, Takeshi Takami, Fumihiko Nakatani, Shojiro Naomi, Toshiaki Nasu (retired in 2006), Tomohiro Sawada, Fuyuki Minagawa, Osamu Haraguchi, Norifumi Kondo, Hiroyuki Shono, Hiromichi Sugiyama, Takeshi Matsuo, Minoru Takaoka, Tamio Nakajima, Masamitsu Toihata, Kozaburo Matsuyama, Kenichi Komori, Toshio Tsubokura, Madoka Taguchi, Yuko Hiramori, Hiroto Okubo, Akihiro Iemura, Osamu Doi, Masayuki Ogihara, Kenji Misumi, Koji Seo, Ken Iwai, Masatoshi Naito, Seiji Ozawa, Kotaro Minoda, Hiromi Fujii, Kimiaki Miwa, Genshi Egusa, Isao Yasuda, Michiaki Ueda, Junichi Miyata, Midori Yoshimura, Masakuni Uemyama, Katumi Watanabe, Yoshikuni Haraguchi, Satoshi Tanazawa, Yoshiaki Osamura, Junji Shibata, Takashi Ono, Syuichi Kamijikkoku, Kazumi Yoshimoto, Etsuo Kinuwaki, Kazuo Kozuma, Kenji Onoue, Yukitaka Nakano, Nanami Abe, Haruo Araki, Kyoji Takaoka, Chieko Imamoto, Hisakazu Suefuji, Keisuke Sugimoto, Terufumi Matsunaga, Akiko Oya, Yoko Onishi, Keizo Kajiwara, Tetsuo Ikuno, Michiaki Doi, Toshiro Igaki, Hiroshi Bando, Tateo Ogura, Kenichi Doijiri, Taisuke Iwaoka, Kazunobu Akahoshi, Kenji Obata, Hisashi Shimono, Kaoru Tsuda, Shinya Yumoto, Keishiro Oka, Hironori Hasegawa, Hisao Fujimoto, Toshiya Atsumi, Akira Matsutani, Yohiyuki Katsuyama, Ryo Fukami, Yoshihisa Iseri, Yutaka Ishibashi, Kiyotaka Kudou, Tetsuo Kuwahara, Kazutaka Maeda, Akira Maki, Naoki Manda, Hirofumi Yasue, Yuji Mizuno, Sueo Momosaki, Koji Tokube, Fumishi Tomita, Tatsuaki Tsuchiya, Matahiro Yabuta, Hidei Yamada, Seigo Sugiyama.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2013.03.015.

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